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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/580,329 | 05/24/2006 | Qiu-Ping Qin | OHMAN-010 | 5669 |

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| EXAMINER | |
|---|---|
| GRUN, JAMES LESLIE | |
| ART UNIT | PAPER NUMBER |
| 1641 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/580,329 | QIN ET AL. | |
| | Examiner | Art Unit | |
| | JAMES L. GRUN | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17-22,27,28,30,33 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-21,27,28,30,33 and 34* is/are rejected.

7)☒ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/11/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The amendment filed 05 December 2009 is acknowledged and has been entered. Claims 1-16, 23-26, 29, 31, and 32 have been cancelled. Claims 17-22, 27, 28, 30, 33, and 34 remain in the case.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 17-21, 27, 28, 30, 33, and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. As set forth, applicant does not teach an antibody that binds to PAPP-A only when complexed to proMBP, the specification teaches antibodies that bind to proMBP whether it is complexed to PAPP-A and/or angiotensinogen and/or complement C3dg (see e.g. Christiansen et al. (Clin. Chem. 46: 1099, 2000)). For these reasons of record, only antibodies binding to PAPP-A or the proMBP components of the PAPP-A/proMBP complexes, but not the full breadth of the

claims, meet the written description and enablement provisions of 35 U.S.C. §112, first paragraph.

Applicant's arguments filed 05 December 2009 have been fully considered but they are not deemed to be persuasive.

Applicant urges that an antibody specific for binding the PAPP-A subunit of the PAPP-A / proMBP complex will detect both free PAPP-A and PAPP-A when complexed. Applicant's argument is not found persuasive because applicant's argument supports the examiner's argument in the prior rejection, i.e. an antibody that binds **both** free PAPP-A and PAPP-A when complexed is not one that binds PAPP-A **only** when complexed. As set forth, only antibodies binding to the proMBP components of the PAPP-A/proMBP complexes are taught as functional for binding, indirectly, to PAPP-A when it is complexed and such disclosure does not describe and enable other than antibodies binding to the proMBP components of the PAPP-A/proMBP complexes as functional in the method.

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27, 28, 30, 33, and 34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 27 and claims dependent thereupon, it is not clear what applicant intends as the marker because it is not clear if the recited ratios are the alternative to free PAPP-A of which the marker consists; the examiner would suggest --said marker consists of free PAPP-A . . . (proMBP), or said marker consists of a ratio . . .-- or --said marker either consists of free PAPP-A . . . (proMBP), or consists of a ratio . . .--. These claims are also not clear in the recitation of "an amount of a marker present" for the implicit alternative in which a ratio is determined, --a value-- is suggested.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 27 and 28 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Conover et al. (US 6,500,630) for reasons of record. As set forth, the reference teaches: determinations of pregnancy-associated plasma protein-A (PAPP-A) as a marker for inflammatory conditions, in particular acute coronary syndromes; the production of monoclonal antibodies specific for PAPP-A not complexed with pro major basic protein (proMBP) and the use of the antibodies for detection of uncomplexed PAPP-A in a sample (see e.g. cols. 4 and 6); and, an assay for PAPP-A activity, inherently measuring the free active form, wherein the enzyme is captured with an antibody and reacted with substrate (see e.g. col. 7).

Applicant's arguments filed 05 December 2009 have been fully considered but they are not deemed to be persuasive.

As set forth, and notwithstanding applicant's assertions to the contrary in the prior declaration of Dr. Pettersson and in applicant's response, the disclosure of Conover et al. is not limited to that which is specifically exemplified. Moreover, as set forth, the reference teaches selection of antibodies "to identify antibodies having specific binding affinity for epitopes of PAPP-A that are not accessible in the specific complex of PAPP-A and proMBP." Thus, applicant's assertions that the reference only teaches antibodies binding to total PAPP-A were again not found persuasive.

Applicant's re-assertions regarding the lack of specificity of an enzymatic antibody capture assay for the detection of free PAPP-A were again not found persuasive for the reasons of record. Applicant's attention is drawn to col. 7, lines 29-37, of the reference combined with the antibody disclosures of cols. 4 and 6, not to the assay disclosed at col. 7, lines 38-44, as argued by applicant. The examiner would also note the disclosures of Overgaard et al. (WO 00/54806 and US 7,115,382) and Overgaard et al. (JBC 275: 31128, 2000) regarding the presence of about 1% or less of uncomplexed PAPP-A in pregnancy plasma and serum (see e.g. US 7,115,382, col. 5). Thus, residual enzymatic activity in a "highly purified" complex may be dependent upon the purification scheme and if complete separation from uncomplexed PAPP-A was achieved or not. Moreover, because Overgaard et al. (JBC 275: 31128, 2000) would suggest that "free" PAPP-A is present as a dimer, it is not clear that the uncomplexed PAPP-A in a hypothetical 2:1 PAPP-A / proMBP complex would not be considered as free.

In response to applicant's argument that the reference fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a noncompetitive sandwich immunoassay) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute for the reasons set forth above.

The declaration under 37 CFR 1.132 filed 05 December 2009 by Qiu-Ping Qin and Kim Pettersson regarding the authorship of the publication of Qin et al. (Clin. Chem. 51: 75, 2005) and the inventorship of the instantly claimed invention has been fully considered.

Claim 22 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Overgaard et al. (WO 00/54806) teach the production of monoclonal antibodies specific for pregnancy-associated plasma protein-A (PAPP-A) not complexed with pro major basic protein (proMBP) and the use of the antibodies for detection of uncomplexed PAPP-A in a sample (see e.g. page 6). The reference also teaches that recombinant PAPP-A can be produced

in cells devoid of proMBP production, such as human embryonic kidney 293T cells, and detected with available antibodies specific for PAPP-A that also bind PAPP-A/proMBP complexes (see e.g. pages 6-7 and 28). Expression of recombinant PAPP-A in a human cell that does not produce proMBP and assay of culture supernatant fluid, i.e. a person's sample, is considered herein as making complexes "non-capable of participating" in the PAPP-A assay.

Overgaard et al. (US 7,115,382) teach the production of monoclonal antibodies specific for pregnancy-associated plasma protein-A (PAPP-A) not complexed with pro major basic protein (proMBP) and the use of the antibodies for detection of uncomplexed PAPP-A in a sample (see e.g. col. 5 and Claim 1). The reference also teaches that recombinant PAPP-A can be produced in cells devoid of proMBP production, such as human embryonic kidney 293T cells, and detected with available antibodies specific for PAPP-A (see e.g. cols. 5-6 and 22-23). Expression of recombinant PAPP-A in a human cell that does not produce proMBP and assay of culture supernatant fluid, i.e. a person's sample, is considered herein as making complexes "non-capable of participating" in the PAPP-A assay.

Overgaard et al. (JBC 275: 31128, 2000) teach proMBP as an inhibitor of PAPP-A enzymatic activity.

Christiansen et al. (Clin. Chem. 46: 1099, 200) teach detection of angiotensinogen /proMBP complexes.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR REPLY TO THIS FINAL ACTION IS SET TO EXPIRE **THREE MONTHS** FROM THE MAILING DATE OF THIS ACTION. IN THE EVENT A FIRST REPLY IS FILED WITHIN **TWO MONTHS** OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE **THREE-MONTH** SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR REPLY EXPIRE LATER THAN **SIX MONTHS** FROM THE MAILING DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 11 a.m. to 7 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, SPE, can be contacted at (571) 272-0806.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/J. L. G./
James L. Grun, Ph.D.
Examiner, Art Unit 1641
March 10, 2010

/Shafiqul Haq/
Primary Examiner, Art Unit 1641